Complete Summary

GUIDELINE TITLE

The pharmacologic management of chronic obstructive pulmonary disease.

BIBLIOGRAPHIC SOURCE(S)

Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group. The pharmacologic management of chronic obstructive pulmonary disease. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2002 Sep. 31 p. [157 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic obstructive pulmonary disease

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Pulmonary Medicine

INTENDED USERS

Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing

TARGET POPULATION

Patients with chronic obstructive pulmonary disease

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation

1. Patient history (smoking history, symptoms, environmental/occupational exposure)
2. Physical examination
3. Spirometry
4. Other tests, including electrocardiogram, arterial blood gas analysis, chest x-ray

Non-pharmacologic Management

1. Patient education
2. Smoking cessation
3. Regular exercise
4. Providing nutritional support, including encouraging weight reduction if necessary
5. Consultation with pulmonary specialist, if necessary

Pharmacotherapy (General Principles and Long-term Therapy)

1. Immunization with influenza and pneumococcal vaccines
2. Long-term oxygen therapy
3. Consideration of drug delivery systems and patient education in their use (e.g., metered dose inhalers with spacers, drug powder inhalers) or use of nebulizers in patients unable to use inhalers
4. Avoidance of drugs that exacerbate chronic obstructive pulmonary disease
5. Short-acting $beta_2$-adrenergic agonists (e.g., albuterol)
6. Long-acting $beta_2$-adrenergic agonists (e.g., salmeterol, formoterol)
7. Oral $beta_2$-adrenergic agonists
8. Anticholinergics (e.g., ipratropium bromide)
9. Combination of $beta_2$-adrenergic agonist and ipratropium bromide (e.g., Combivent®, DuoNeb®)
10. Theophylline

11. Inhaled corticosteroids (e.g., budesonide, flunisolide, triamcinolone, beclomethasone, fluticasone)
12. Oral corticosteroids
13. Leukotriene inhibitors (e.g., zafirkulast)

Management of Acute Exacerbations

1. Evaluation of signs and symptoms of exacerbation
2. Use of bronchodilators (inhaled short-acting beta$_2$-adrenergic agonists, inhaled ipratropium or combination therapy)
3. Systemic corticosteroids (intravenous methylprednisolone, oral prednisone)
4. Antibiotic therapy (amoxicillin, doxycycline, trimethoprim/sulfamethoxazole, quinolones, amoxicillin-clavulanate, cephalosporins, newer macrolides)
5. Sputum culture
6. Theophylline

MAJOR OUTCOMES CONSIDERED

- Improvement in symptoms
- Rate of decline of pulmonary function (e.g., forced expiratory volume in one second)
- Patient functioning and patient satisfaction
- Frequency and severity of exacerbations and related clinic and hospital visits as caused by chronic obstructive pulmonary disease
- Adverse effects of medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Development of the guidelines relied upon the following consensus documents:

- Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. NHLBI/WHO workshop report. www.goldcopd.com
- Bach PB, Brown C, Gelfand SE, American College of Physicians-American Society of Internal Medicine; American College of Chest Physicians. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001; 134:600-20.
- American Thoracic Society Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 1995; 152:S78-S121.
- British Thoracic Society Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52(suppl 5): Sl-S28.

- Siafakas NM et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD): A consensus statement of the European Respiratory Society (ERS). Eur Respir J 1995; 8:1395-1420.
- Department of Veterans Affairs Clinical Practice Guidelines for the Management of Persons with Chronic Obstructive Pulmonary Disease or Asthma. Publication No. 99-0012.

The algorithm and annotations are in part based on the chronic obstructive pulmonary disease (COPD) guideline developed in 1999. A literature search of MEDLINE was conducted combining the search terms chronic obstructive pulmonary disease and COPD with the following: beta adrenergic agonists, albuterol, salbutamol, metaproterenol, pirbuterol, bitolterol, salmeterol, formoterol, ipratropium, theophylline, inhaled corticosteroids, inhaled steroids, corticosteroids, steroids, fluticasone, budesonide, beclomethasone, flunisolide, triamcinolone, prednisone, methylprednisolone, acute exacerbation, antibiotics. The literature was limited to clinical trials, adult human subjects and articles published in the English language. Using this strategy, 102 clinical trials were found. Nineteen were used in the development of this guideline. The others were excluded for the following reasons: drug or formulation not available in the United States (n=15), ventilator-related articles (n=11), outside the scope of the document (n=30), small studies or studies of short duration where larger and/or longer duration studies available (n=15), studies involving inflammatory or cellular mediators, etc. (n=7), asthma study (n=1), other (n=4). The bibliographies of articles and consensus documents were reviewed for additional relevant literature. Literature known to the Pharmacy Benefits Management and Medical Advisory Panel (PBM-MAP) on medical history, physical examination, diagnosis, and evaluation was also included in the document.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus
Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

A
Large, randomized trials with clear-cut results (low risk of error)

B
Small, randomized trials with uncertain results (moderate to high risk of error)

C
Nonrandomized, historical and expert opinions; uncontrolled studies, case series

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Whenever possible, the Pharmacy Benefits Management and Medical Advisory Panel relies upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of Veterans Affairs guidelines. Relevant literature is reviewed and assessed with consideration given to the Veterans Affairs population. Draft guidelines are sent to the field for comments prior to being finalized.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

I
Usually indicated, always acceptable, and considered useful and effective.

IIa
Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.

IIb
Acceptable, of uncertain efficacy and may be controversial. Not well established by evidence, can be helpful, and probably not harmful.

III
Not acceptable, of uncertain efficacy, and may be harmful. Does not appear in the guidelines.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were disseminated for peer-review through the Veterans Integrated Service Networks (VISNs), prior to their completion. A partial list of individuals who reviewed the guideline is included in the original guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for the pharmacologic management of chronic obstructive pulmonary disease (COPD) are organized into 2 major algorithms, the first addressing outpatient pharmacotherapy of COPD and the second addressing acute exacerbation. The strength of recommendation (SR) grading (I-III) and level of evidence (LE) grading (A-C) are defined at the end of the "Major Recommendations".

I. Definition

Chronic obstructive pulmonary disease (COPD) is characterized by the presence of airflow obstruction, principally due to chronic bronchitis or emphysema. The airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible.

II. General Principles

A. Epidemiology

COPD is the fourth leading cause of death in North America and its mortality rate is rising. It is estimated to affect 15 million Americans, and the prevalence is increasing. It affects 4 to 6% of adult males and 1 to 3% of adult females in the U.S.

In 1996 within the Department of Veterans Affairs (VA), more than 126,267 patients were discharged with a primary or secondary diagnosis of obstructive lung disease. This accounted for approximately 33% of all patients admitted to medical services and approximately 16% of all VA hospital admissions. In the outpatient setting, approximately 1 million visits had obstructive lung disease listed as a primary or secondary diagnosis.

B. Risk and Prognostic Factors

1. Tobacco smoking accounts for 80 to 90% of the risk of developing COPD.
2. Smoking is a greater risk factor for developing COPD than are occupational exposures.
3. Alpha1-antitrypsin deficiency is a rare, but important cause of early onset COPD.
4. Age, forced expiratory volume in 1 second (FEV_1), severity of hypoxemia, presence of hypercapnia, and cor pulmonale are prognostic factors.

III. Patient Evaluation

The diagnosis of COPD should be considered in patients with a current or prior history of chronic cough present intermittently or daily, current or prior history of chronic sputum production, dyspnea, and history of significant exposure to risk factors (tobacco, occupational/environmental exposure).

Alpha1-antitrypsin (AAT) deficiency accounts for less than one percent of COPD. AAT deficiency may be suspected in patients with moderate-severe COPD before the age of 50, a family history of AAT, chronic bronchitis with airflow obstruction in a person who has never smoked, bronchiectasis, in the absence of clear risk factors, or cirrhosis without apparent risk factors. Referral to specialist should be considered.

A. History
   1. Smoking history: Age at initiation, pack-year history, smoking cessation history, current smoking status, and willingness to quit
   2. Extent, severity, frequency and duration of symptoms: cough, dyspnea, sputum volume and character, wheezing, and activity limitation
   3. Environmental and occupational exposure history

B. Physical Examination

   The sensitivity of physical examination is low for diagnosing mild or moderate COPD. Physical signs of COPD include wheezing, prolonged forced expiratory time, decreased breath sounds, decreased ribcage expansion and diaphragmatic excursion, thoracic hyperresonance, subxiphoid cardiac apical impulse, and use of accessory muscles. However, the presence or absence of these signs does not clearly reflect the degree of airflow limitations.

C. Spirometry

   Measurement of FEV_1 is important to establish airway obstruction, define severity, indicate prognosis, and measure response to therapy and progression of disease. Spirometry (pre- and post-bronchodilation) is required to confirm presence and reversibility of airflow obstruction and to quantify the maximum level of ventilatory function. Peak expiratory flow rate (PEFR) is not as accurate as FEV_1 in assessing lung function or airway obstruction in COPD and may underestimate the degree of airflow obstruction.

D. Other Tests
   1. Electrocardiogram (ECG): ECG helps indicate the presence of late cor pulmonale.
   2. Arterial Blood Gas: A resting arterial blood gas after 30 minutes on room air remains the standard for determining the need for oxygen therapy. It also is important for the diagnosis of respiratory failure.
   3. Chest x-ray (CXR): CXR can detect lung hyperinflation, bullae, pulmonary hypertension, cor pulmonale, and pneumothorax. It is suggestive of emphysema when the disease is severe and

may be helpful when the disease is moderate. It is also used to help exclude other pulmonary diseases.

III. Management of COPD

A. General Approach

1. Management of stable COPD aims to avoid or minimize adverse effects of treatment, reduce symptoms, prevent and treat complications, prevent and treat exacerbations, reduce the decline in lung function, improve quality of life, and increase survival.
2. It is important to educate the patient and family about the disease and treatment; encourage an active, healthy lifestyle; obtain agreement of goals in treatment; and provide supportive follow-up. Cooperative self-management should be fostered.
3. Principles of management include smoking cessation, bronchodilation, suppression of inflammation, treatment of infection, mobilization of secretions, and support with oxygen to maintain adequate oxygenation.
4. For the primary care provider, a pulmonary specialist consult should be considered for unstable disease not controlled by therapy, frequent hospital admissions, difficult treatment decisions, such as instituting oral or high dose inhaled corticosteroids, etc. The threshold for consultation should depend on the level of expertise of the provider. Once stable, the patient should be referred back to the primary care physician for long-term management.

B. Nonpharmacologic Therapy

1. Smoking cessation

Smoking cessation can reduce the rate of decline in FEV_1 to near that in nonsmokers. As the only disease modifying intervention available, it should be emphasized at each clinic visit LE=A, SR=I. Patients should be encouraged to participate in an intensive smoking cessation program. Nicotine replacement in conjunction with a comprehensive therapy program can be an effective strategy, with a smoking cessation success rate of 20 to 40% at 6 months in some studies. Other agents with evidence of benefit in smoking cessation include bupropion and nortriptyline. A full review of agents used in smoking cessation is beyond the scope of this guideline. For a full review, refer to the Veterans Health Administration and Department of Defense (VHA/DoD) guideline on smoking cessation and the U.S. Public Service report for treating tobacco use and dependence.

2. Regular exercise

An informal program, with an emphasis on walking and upper body exercise, may help maintain physical functioning. In more advanced disease, formal exercise training can be part of a comprehensive rehabilitation program that may be beneficial.

3. Nutritional support

Undernutrition is associated with respiratory muscle weakness and increased mortality. The most cost-effective method for nutritional support in undernourished patients has not been established. It is important in nonobese COPD patients to prevent weight loss. For any patient with poor appetite or eating-related dyspnea, frequent small meals may be more tolerable. Weight reduction should be encouraged in obese patients.

C. Pharmacotherapy

1. General considerations

a. Immunization with influenza vaccine is recommended by the Centers for Disease Control and Prevention (CDC) and should be administered annually LE=A, SR=I. Evidence showing benefit with pneumococcal vaccination in COPD patients is controversial. Pneumococcal vaccine is administered once at diagnosis if over age 65, otherwise at diagnosis and at age 65, provided at least 6 years have elapsed since the first dose was LE=B, SR=IIa. Vaccination should be encouraged if the patient does not have contraindications.

b. Need for long-term oxygen therapy should be evaluated. Long-term oxygen therapy has been shown to increase survival in patients with resting hypoxemia and can increase exercise performance and activities of daily living, improve mental functioning, alleviate right heart failure due to cor pulmonale, augment cardiac function, reverse secondary polycythemia, and increase body weight. Patients should be educated on the benefits of oxygen therapy and survival. Refer to VHA guidelines on long-term oxygen therapy.

c. Because of a lower incidence of systemic adverse effects, inhaled bronchodilators are preferred to oral bronchodilators. The amount of inhaled medication deposited in the lung is in direct relation to technique; therefore, providing education on the proper technique in the use of metered dose inhalers (MDI) is necessary. (Refer to Appendix 1 in the original guideline document). The aerosol actuator that comes with a given product should only be used with that product and not used with other aerosol medications. Spacers should be encouraged, to enhance drug delivery. Complicated inhaler regimens should be avoided as patient adherence to therapy declines. Consider other drug delivery systems (e.g., dry powder inhalers) if patient cannot use an MDI with spacer.

d. There is little evidence that nebulizer delivery offers improvement in the management of stable COPD over that of an MDI with spacer. Patients who may benefit from drug delivery via nebulizer are those who have

difficulty in using a MDI with a spacer device or other drug delivery systems such as dry powder inhaler devices. The following are examples of patients who may be unable to use a MDI or dry-powder inhaler: those with impaired hand strength or dexterity, visual impairment, mental/cognitive problems, or inability to use an MDI during an acute exacerbation. Nebulizer delivery should be continued only if there is a clear clinical benefit LE=B, SR=I.

e. Drugs that can exacerbate COPD should be avoided; however, in some situations where the benefits of using the drug outweighs the risk (e.g., selective $beta_1$-blockers post myocardial infarction [MI]), the drug may be cautiously administered. It should be noted that patients with COPD have largely been excluded from clinical trials of beta-blocker therapy. If beta-blockers (selective or nonselective) are used, pulmonary function and symptoms must be monitored closely LE=C, SR=IIa.

2. Adrenergic agonists

a. Short-acting $beta_2$-adrenergic agonists

1. Available in MDI, dry powder inhalers, nebulizer and oral forms (Refer to Appendix 2 in the original guideline document). They can improve function and health-related quality of life.
2. Short-acting, selective $beta_2$-agonists are preferred over the nonselective agents because of demonstrated efficacy, rapid action, and selective action on airways. All short-acting agents have similar efficacy and selection could be based on cost.
3. Short-acting $beta_2$-agonists should be used as needed ("prn") for the majority of symptomatic patients with COPD. LE=B, SR=1I. These agents may also be administered on a scheduled basis for those patients uncontrolled on ipratropium alone. Interestingly, one small study has recently shown that ipratropium plus albuterol (using separate inhalers) administered on a scheduled basis is no better than ipratropium plus "prn" albuterol. A larger study confirming these findings is needed.
4. The usual maximum dose is 12 puffs per day for short-acting agents such as albuterol. The usual single dose of albuterol is 2 puffs. Data concerning added benefit from using more than 2 puffs are variable and was not found in all studies.
5. Symptoms may improve without substantial improvement in FEV_1 indicating that continuation of therapy does not depend on routine assessment with spirometry. Patients should be treated with bronchodilators regardless of

whether or not there is improvement in FEV_1 following bronchodilator administration.

b. Long-acting agent $beta_2$-adrenergic agonists

1. Salmeterol and formoterol are approved for use in COPD.
2. Both salmeterol and formoterol have been compared to ipratropium in 12-week studies. Two studies found no difference between salmeterol and ipratropium in reducing "as needed" beta-agonist use, health-related quality of life, patient self-assessment of symptoms (shortness of breath, chest tightness, and cough). Additionally, Rennard found no difference in exacerbation rates and FEV_1 area under the curve (AUC) between ipratropium and salmeterol. Mahler on the other hand found a higher FEV_1 AUC, lower exacerbation rate, and decreased nighttime shortness of breath with salmeterol.

   Formoterol and ipratropium increased the 12-hour FEV_1 AUC, though the changes with formoterol were statistically greater than with ipratropium. Formoterol 12 micrograms achieved a clinically significant improvement in quality of life scores and reduced the number of "as needed" doses of albuterol compared to ipratropium.

   In all 3 studies, the patients who had reversibility to albuterol (>12% and 200 mL increase in FEV_1) had a greater response than those who were considered albuterol unresponsive. Also, ipratropium was dosed as 2 puffs four times a day (qid), which is generally considered a low dose.

   Only one study has looked at combining ipratropium with a long-acting $beta_2$-adrenergic agonist versus the $beta_2$-adrenergic agonist alone. There was added improvement in airway obstruction when salmeterol and ipratropium were combined compared to salmeterol alone. However, the combination did not further improve symptom scores or need for rescue albuterol.

3. Both salmeterol and formoterol have been compared to theophylline. Monotherapy with the long-acting $beta_2$-agonists were superior to theophylline monotherapy in improving pulmonary function and reducing rescue medication use.

The combination of salmeterol and theophylline titrated to a peak concentration of 10 to 20 micrograms/mL resulted in improved lung function, decreased symptoms and use of rescue medications, and greater patient satisfaction when compared to either agent given alone. However, adverse events were greater in patients receiving theophylline.

4. The role of long-acting beta$_2$-adrenergic agonists in the scheme of COPD therapy needs to be better defined. Potential roles for salmeterol or formoterol include:
    - Patients using ipratropium and requiring 12 or more puffs a day of a short-acting beta$_2$-agonist
    - Patients who have troublesome, nocturnal dyspnea
    - Patients requiring maintenance ipratropium but unable to comply with qid dosing or doses requiring a large number of puffs per day.
    - Should be considered for patients with suboptimal response to scheduled ipratropium and short acting beta agonists before using theophylline.

    Salmeterol or formoterol should only be continued in those patients who experience symptomatic benefit from its addition to their regimens.

5. Because of the slow onset of effect, salmeterol should not be used for acute shortness of breath. Although formoterol has a rapid onset of action similar to albuterol, it should not be used to treat acute dyspnea as additional dosing for acute events may result in side effects from the excess beta$_2$-agonist. The short-acting agents should be used for relief of acute symptoms.
6. Use the long-acting beta$_2$-adrenergic agonists cautiously in patients with preexisting cardiac arrhythmias and partial pressure of oxygen (PO_2) <60 mm Hg. One small study showed that the number of isolated supraventricular premature beats and ventricular premature beats were increased with salmeterol and formoterol. Formoterol 24 micrograms produced more premature beats and reduced serum potassium to a greater extent than salmeterol 50 micrograms and formoterol 12 micrograms.

7. Doses higher or more frequent than salmeterol 50 micrograms twice a day (bid) or formoterol 12 micrograms bid have not been shown to be more efficacious and in some studies have actually resulted in lower quality of life scores.

c. Oral $beta_2$-agonists

Can be useful for patients who cannot use any inhaled form, although such cases are rare. The risk of systemic adverse reactions is increased significantly with these oral agents (Refer to Appendix 3 in the original guideline document).

3. Anticholinergics
   a. Ipratropium bromide, the prototype anticholinergic bronchodilator, is available as both an MDI and a nebulizer solution (Refer to Appendix 2 in the original guideline document).
   b. Ipratropium bromide and $beta_2$-agonists have similar efficacy. It may cause less severe systemic side effects than the $beta_2$-agonists due to minimal systemic absorption.
   c. Ipratropium has a slower onset and longer duration of action than the short-acting $beta_2$-agonists.
   d. Use a trial of ipratropium for scheduled dosing in asymptomatic patients with FEV_1 <50% predicted. At this degree of obstruction, dyspnea is usually present. However, a lack of, or masking of symptoms may be the result of patients avoiding activities and adapting to his/her disability, or the patient may perceive dyspnea as part of the natural aging process. Ipratropium should only be continued in patients where there is evidence of improvement in masked symptoms (e.g., the patient begins to engage in some activities that in the past were avoided or associated with dyspnea) LE=C, SR=1I.
   e. Ipratropium should be used in patients who have daily symptoms LE=A, SR=I.
   f. In patients with COPD, ipratropium bromide, at peak effect, typically increases the FEV_1 by 0.15 to 0.35 L.
   g. Dosage is 2 to- 4 puffs four times daily. Some dose-response studies suggest that dosages higher than the manufacturer´s recommendations might be needed to produce maximal improvement in pulmonary function. Improvement in level of physical functioning can be used to guide therapy.
   h. Patients with glaucoma should use a spacer to avoid spraying the agent into their eyes.
   i. Although ipratropium bromide is minimally absorbed, it should be used with caution in patients with closed angle glaucoma or other conditions potentially worsened by the drug´s anticholinergic action.

j. A new drug application for tiotropium, a once daily anticholinergic, is anticipated to be filed with the Food and Drug Administration in the near future.

4. Combination therapy
   a. The combination of a beta$_2$-agonist and ipratropium bromide is advised for patients with chronic COPD whose symptoms are inadequately controlled with one agent. The combination of agents in adequate doses may provide a synergistic effect and lessen the risk of adverse effects from higher doses of a single agent LE=A, SR= I.
   b. Combivent® is a product that provides albuterol 90 micrograms and ipratropium 18 micrograms per puff, in one metered dose inhaler. This product should not be used as a first-line agent. It may be considered for patients who are well controlled on both individual agents in combination or for those patients requiring ipratropium with scheduled albuterol where adherence to therapy might be improved.

      Although Combivent can be safely used as rescue therapy, it is not generally recommended due its significantly higher cost than that of albuterol.

      A combination product for nebulizer use (DuoNeb®) is also available and provides albuterol 2.5 mg (as the base) and ipratropium 0.5 mg in a single 3 mL unit dose vial. Alternatively, a combination can be made by mixing 0.5 mL of albuterol solution with 2.5 mL of ipratropium solution to provide 2.5 mg and 0.5 mg respectively.

5. Theophylline
   a. Theophylline may be added if response to inhaled bronchodilators is inadequate; however, the clinician should first analyze the risk/benefit ratio. It should be continued only for patients who have a beneficial response (e.g., improvement in pulmonary function, arterial blood gas symptoms, or exercise performance) LE=B, SR=IIa.
   b. Several theophylline preparations are available (Refer to Appendix 4 in the original guideline document). The slow-release, once-a-day formulations taken at night provide longer control, and may be of benefit for nocturnal dyspnea.
   c. Theophylline has a narrow therapeutic index with a high risk of dose-related adverse reactions, especially in older patients. Adverse effects of theophylline include insomnia, anxiety, nausea, vomiting, tremor, palpitations, arrhythmias, delirium, and seizures. Older patients have increased susceptibility to chronic theophylline toxicity.

d. Drug interactions and other factors altering theophylline metabolism are numerous (Refer to Appendix 4 in the original guideline document).
e. Due to toxicity, the use of theophylline as monotherapy in COPD should be restricted to rare cases where patients cannot adequately administer inhalers or nebulizers LE=B, SR=IIa.
f. Dosage should be carefully adjusted to achieve a peak plasma concentration between 5 to 12 micrograms/mL. If there is minimal or no response, increase the dose to achieve levels between 8 to 15 micrograms/mL, provided the patient can tolerate the increase. This can be effective in increasing FEV_1 with less risk of adverse effects (Refer to Appendix 4 in the original guideline document). A peak concentration at the lower end of the range is recommended in elderly patients and in patients who have risk factors for reduced clearance. In general, serum levels for product administered every 12 hours can be obtained 3 to 7 hours after the morning dose. For the once daily products, the serum level can be obtained 8 to 12 hours after the dose.
g. Measure the serum theophylline concentration at the start of therapy when steady state is achieved, when pulmonary symptoms change, acute illness develops, interacting drugs are added or discontinued, noncompliance is suspected, dosage adjustments are made, or immediately after symptoms suggestive of toxicity develop.

6. Corticosteroids
a. Recent evidence has better defined the role of inhaled steroids in the management of COPD. Four large, long-term randomized controlled trials were unable to show that chronic use of inhaled steroids reduces the rate of decline in FEV_1. This was demonstrated in patients with all levels of severity of COPD.
b. Long-term use of high-dose inhaled steroids in patients with moderate-severe COPD may reduce the frequency or severity of exacerbations, and unscheduled clinic care. One study also showed better health-related quality of life scores for patients receiving inhaled steroids.
c. Patients with mild COPD did not show improvement in exacerbation rates or symptoms when lower doses of inhaled steroids (budesonide 800 micrograms/day) were used. Whether the use of high-dose inhaled steroids in this group is beneficial is unknown.
d. The decision to institute a steroid trial in patients with COPD should be based on familiarity and experience of the provider. Pulmonary referral may be requested at the provider's discretion.
e. Patients with moderate-severe disease with frequent exacerbations may be considered for an inhaled steroid response trial. The trial should be instituted only when

the patient is stable, and is failing maximum bronchodilator therapy LE=A, SR=IIa.

f. It is common practice to give a patient a short trial of oral steroids and then attempt a switch to inhaled steroids in those who respond. The guideline developers do not recommend this practice since the response to an oral steroid trial is not helpful in predicting a response to inhaled steroids.

g. There is no uniform definition or criteria for what constitutes a response to an inhaled steroid trial. According to published data, improvement in spirometry is generally not expected. Although not expected, improvement in spirometry may occur and, on a case by case basis, should be measured to help guide therapy. Outcomes to consider include improvement in symptoms, frequency and severity of exacerbations, and related clinic and hospital visits.

h. A six-week trial of high dose inhaled steroids is adequate to evaluate symptomatic response; however, to see improvement in exacerbation rates or severity, a longer trial may be necessary (e.g., 6 months). If a patient does not respond adequately to the trial, consider tapering and discontinuing the steroid.

i. Although there are no data whether patients with moderate-severe COPD benefit from lower doses of inhaled corticosteroids, lowering the dose may be attempted to see if response is maintained. Use of lower-dose inhaled steroids may lessen the risk of osteoporosis and adrenal suppression.

j. Pulmonary status may deteriorate when inhaled steroids are withdrawn from patients who were receiving maintenance therapy with these agents.

k. Inhaled corticosteroids should be administered with the aid of a spacer, unless contrary to manufacturer´s specifications. Gargling with water after each oral steroid dose may help prevent oropharyngeal candidiasis. Patients should be monitored for systemic steroid effects resulting from chronic use of high-dose inhaled corticosteroids.

l. Maximum doses of inhaled corticosteroids vary among agents (Refer to Appendix 5 in the original guideline document).

m. Patients not responding to inhaled steroids may be candidates for a short-term oral steroid trial. Numerous short-term clinical trials (1 to 3 weeks) have shown that oral corticosteroids will increase FEV_1 by 20% or more in approximately 10 to 20% of patients. There are no prospective controlled long-term oral steroid studies in COPD. Two uncontrolled studies demonstrated that long-term oral steroids might decrease the decline in FEV_1 in some patients. Given the unproven benefits and the risk of toxicity, oral steroids should be considered in those

who cannot take or have not responded to inhaled steroids.

Oral steroid trial

- Since short-term (2 to 3 weeks) high-dose steroids usually do not produce serious toxicities, the ideal use is to administer the glucocorticoids in a short "burst" (up to 40 mg/day for 2 to 3 weeks of prednisone).
- A positive response includes symptomatic benefit and an increase in FEV_1>20%.
- In nonresponders, discontinue oral steroid
- It should be remembered that it is not known whether a response to short-term, high-dose oral steroid reliably predicts long-term response
- Combination oral and inhaled steroids may be tried as an oral steroid-sparing measure
- Repeatedly evaluate patients to determine if steroid therapy can be discontinued

For responders, the question remains whether one should continue oral steroids at the lowest possible daily dose or discontinue after the 2-week trial and manage patients with intermittent steroid bursts. One small, randomized VA study looked at whether patients receiving chronic oral steroids can be withdrawn from chronic use and be managed with "on demand" use. Although this study had selection bias, was underpowered, and had a high dropout rate, it did provide preliminary evidence that suggests patients can be withdrawn from chronic steroid use and be treated on demand. It should also be noted that patients in this study were receiving concomitant inhaled steroids. There is insufficient evidence at this time to recommend one single approach. Most practitioners would initially attempt managing patients with intermittent steroid bursts and to reserve chronic low dose steroids for those who have not achieved good control with intermittent treatment.

n. Patients who have received prolonged oral corticosteroid treatment should receive stress doses of steroids during episodes of severe illness or injury. Adrenal insufficiency may persist for up to a year following the discontinuation of chronic steroid therapy. Transfer of a patient from oral to inhaled steroids must be done slowly to avoid risk of adrenal insufficiency. Inhaled corticosteroids, particularly at higher doses, may also predispose the patient to adrenal suppression.
o. Adverse effects of oral corticosteroids are numerous, including hypertension, hyperglycemia, weight gain,

purpura, mental status changes, depression, glaucoma, cataracts, myopathy, and adrenal suppression. Osteoporosis may occur within 6 months.

p. Long-term use (3 years) of high-dose inhaled steroids in patients with COPD showed a 2% decrease in femoral neck bone density. Another long-term inhaled steroid study using lower doses of inhaled steroids showed no changes in bone density. Patients requiring long-term steroids should be evaluated for risk of osteoporosis and be treated preventively with calcium and vitamin D supplements and weight-bearing exercise. The bisphosphonates alendronate and risedronate are FDA approved for prevention and treatment of steroid-induced osteoporosis. The American College of Rheumatology recommends treatment with alendronate or risedronate in patients receiving at least 3 months of prednisone >5 mg/day. No study has addressed using bisphosphonates in patients using long-term inhaled steroids. However, long-term use of inhaled steroids may decrease bone density, particularly when higher doses of the more potent inhaled steroids are used. In such situations, providers might consider obtaining a bone density scan and treat with bisphosphonates for those with osteoporosis or osteopenia. Calcitonin and hormone replacement therapy are other options for preventing or treating steroid induced osteoporosis and should be considered where appropriate. Efficacy is mainly limited to preventing bone loss at the lumbar spine. They are less efficacious at preventing or treating bone loss at the femoral neck. The risks of long-term steroid treatment should be discussed with the patient.

7. Leukotriene inhibitors

The leukotriene believed to mediate inflammation in COPD is LTB_4 and in asthma is LTD_4. Montelukast and zafirlukast do not inhibit the LTB_4 receptor and are therefore not expected to improve pulmonary function and symptoms of COPD. One single dose study of 16 patients (majority who had >12% increased in FEV_1 with albuterol 400 micrograms) with COPD found the following rank order improvement in FEV_1: salmeterol 50 micrograms + zafirlukast 40 mg = salmeterol 50 micrograms > zafirlukast 40 mg > placebo. However, there was a subgroup of 7 patients who had a better response with the combination than with salmeterol alone. There are preliminary data that the leukotriene inhibitors may provide some benefit in those who have partially reversible COPD. Larger and longer term studies are needed before these agents can be routinely recommended. If a trial of leukotriene inhibitor therapy is initiated, it should be continued only if pulmonary function, symptoms, exercise tolerance, or well-being improve.

D. Management of Acute Exacerbations

1. Signs and symptoms of acute exacerbation

There is no uniform definition of COPD exacerbation nor are there standardized validated grading systems for severity. At best, acute exacerbations can be defined as a recent deterioration in the patient´s clinical and functional state, beyond that of normal day-to-day variations of their COPD. In general, worsening dyspnea, increased sputum production, and change in character or color of sputum are the most common features associated with an acute exacerbation. Other findings may include:

- Increased cough
- Fever
- Development of or increase in wheezing
- Cyanosis
- Malaise, fatigue
- Use of accessory muscles
- Decreased exercise tolerance
- Peripheral edema
- Increased respiratory rate
- Loss of alertness altered mental status
- Tachycardia
- Worsening airflow obstruction
- Shallow breathing
- Worsening arterial blood gases

The most common precipitating event is acute bronchitis; however, the differential diagnosis includes pneumonia, pneumothorax, heart failure, pulmonary edema, and pulmonary embolism.

A severe exacerbation is suggested by the following: mental status changes, dyspnea at rest, respiratory rate >25/min, heart rate >110/min, cyanosis, accessory muscle use, pO_2 <60 mmHg on room air. Patients presenting with a severe exacerbation should be referred to the emergency department.

2. Bronchodilators

a. Short-acting inhaled $beta_2$-agonists such as albuterol, are the bronchodilators of choice to treat COPD exacerbations. These agents can be beneficial by improving FEV_1 and dyspnea LE=B, SR=I.
b. Although the maximally effective dose in COPD exacerbation is not known, there are limited data suggesting that 3 to 4 puffs produces significant bronchodilation. The duration of action is shorter during an acute exacerbation; therefore, more frequent administration (every to 1 to 3 hours) may be necessary. The 1995 ATS Consensus Statement concludes that dosages for severe exacerbations may be

as high as 6 to 8 puffs every 1/2 to 2 hours. As symptoms improve, the frequency and or dose can be reduced. Patients who have received instruction on home management of exacerbations should contact the provider if not responding to initial measures.

c. Higher doses of these agents increase the risk of adverse reactions, such as tremor and cardiac arrhythmias. Higher doses of inhaled $beta_2$-agonists should be used cautiously in patients with known coronary artery disease, arrhythmias, or left ventricular dysfunction. An alternative therapy is to combine inhaled ipratropium at higher than usual doses with the $beta_2$-agonist at moderate doses.

d. If the patient is not obtaining the benefit from the MDI with spacer, the $beta_2$-agonist can be given via nebulizer (e.g., albuterol 2.5 mg every 2 to 4 hours). Studies showing equivalency between MDI and nebulized delivery were done primarily in the emergency department or hospital setting LE=A, SR=IIa.

e. Inhaled ipratropium can be used to treat acute exacerbations of COPD. As a single agent, its effect on spirometry is equal to that of inhaled $beta_2$-agonists. While ipratropium can be used to treat exacerbations, its slower onset of action makes $beta_2$-agonists the preferred drug during acute exacerbations LE= B, SR=I.

f. Ipratropium may be dosed at 3 to 4 puffs every 3 to 4 hours. The ATS suggests that doses of 6 to 8 puffs every 3 to 4 hours can be used in severe cases, although a dose-response relationship has not been determined for higher doses of ipratropium in COPD exacerbation.

g. Ipratropium 0.5 mg every 2 to 8 hours via nebulizer can be given to patients who cannot use an MDI with spacer.

h. Combination beta-agonist and anticholinergic has been evaluated in 9 studies; 7 assessed short-term outcomes, 1 looked at outcomes at 24 hours, and 1 inpatient study assessed outcomes up to the time of discharge. Six of the short-term studies, the 24-hour study, and the inpatient study showed no additional benefit in pulmonary function with the combination. These studies were relatively small, so a difference between treatment groups may have been missed. At this time, there is insufficient evidence that the combination provides any short-term advantage over use of single agents LE= B, SR=I.

3. Corticosteroids

a. Recent data has shown that steroid administration improves pulmonary function and decreases relapse rate in patients with acute exacerbations requiring hospitalization. The dosing and duration of treatment varied from study to study, making it difficult to recommend a specific regimen. An example of a

reasonable regimen is intravenous (IV) methylprednisolone at 0.5 mg/kg every 6 hours for 72 hours followed by oral prednisone, for an additional 7 to 10 days LE=A, SR=IIa. In the VA based SCCOPE trial, therapy lasting longer than 2 weeks was not found to be more beneficial than a 2-week regimen. In the SCCOPE trial, hyperglycemia warranting treatment occurred in 15% of patients receiving steroids compared to 4% receiving placebo.

b. There is a paucity of data concerning steroid use for managing acute exacerbations in the outpatient or emergency room setting. It is unclear whether all acute exacerbations merit treatment with systemic corticosteroids. However, the following patients should be considered for systemic steroid treatment: patients on maintenance oral or inhaled steroids; patients who have recently stopped oral steroids; patients who have had a prior response to oral steroids; patients with a low oxygen saturation ($\leq$90%); patients with PEFR $\leq$100 L/min; or patients not responding to initial bronchodilator therapy LE=C, SR=IIa. One study showed that a single dose of IV methylprednisolone 100 mg did not improve FEV_1 or rate of hospitalization over that of placebo. Thompson found that a 9-day course of oral prednisone, administered in a tapering fashion, improved FEV_1, PEF, and pO_2, and decreased relapse rates when compared to placebo. Bullard found that hydrocortisone 100 mg IV every 4 hours resulted in greater increases in peak flow, FEV_1, and ED discharges than placebo LE=A, SR=IIa. The dose, duration, and tapering of therapy for a course of oral steroids remains to be established. Prednisone 0.6 to 0.8 mg/kg/day for 7 to 14 days is often used in clinical practice. No study has looked at whether tapering of the steroid dose is necessary; however, many clinicians include a taper as part of the treatment course LE=C, SR=IIb. Upon completion of a steroid course, the patient must be monitored for potential relapse.

c. Patients already on higher doses of steroids (e.g., prednisone 40 to 60 mg) that have not responded to intensive bronchodilator therapy should be referred for specialist consultation on an emergent basis or for hospital admission.

4. Antibiotic Therapy

a. Antibiotic therapy is not indicated for all acute exacerbations of COPD since viruses or environmental exposures can also result in acute exacerbation.

b. If the exacerbation is associated with changes in sputum (quality, volume, or color) and increased dyspnea, cough, or fever, treatment with antibiotics is reasonable LE=B, SR=I. Presence of an infiltrate on chest

radiograph suggests pneumonia; the patient should be treated with antibiotics as deemed appropriate.

c. Older patients or those with severe underlying lung dysfunction are most likely to benefit from antibiotic therapy. However, one retrospective review at Veterans Affairs Medical Center found that patients treated with antibiotics had a lower relapse rate than those who did not receive antibiotics and that severity of the exacerbation or the underlying disease was not predictive of relapse.
d. The most commonly isolated bacteria include Haemophilus influenza, Moraxella catarrhalis, and Streptococcus pneumoniae.
e. Sputum cultures, carefully obtained, may be helpful, especially in patients who have failed to respond to initial empiric antimicrobial therapy. Choice of antibiotic should consider local sensitivity patterns and patient allergies. In areas where resistance is not a problem, established antibiotics, such as amoxicillin, doxycycline, or trimethoprim/sulfamethoxazole, may be used. One VA study conducted in San Antonio found a higher relapse rate in patients receiving amoxicillin. The optimal duration of treatment is unknown; however, many clinicians choose a 7 to 14 day course.
f. The newer antibiotics, such as quinolones, amoxicillin-clavulanate, 2nd or 3rd generation oral cephalosporins, or the newer macrolides should be reserved for special situations: treatment failure with conventional agents, recent hospitalizations, nursing home residents, advanced COPD, pneumonia, or bacterial isolate resistant to older established antibiotics.

5. Theophylline
    a. Due to minimal evidence of efficacy and potential risk of toxicity, the role of theophylline in acute COPD exacerbation is questionable. In general, if the patient is not on theophylline, there is no need to start it in the setting of an acute exacerbation LE=B, SR=IIb.
    b. If the patient is already on theophylline, adjust the dosage, as necessary, to achieve a serum concentration of 5 to 12 micrograms/mL. Keep in mind that certain factors such as antibiotics or fever can alter theophylline concentrations. (Refer to Appendix 4 in the original guideline document)

Strength of Recommendation

Level I: Usually indicated, always acceptable, and considered useful and effective.

Level IIa: Acceptable, of uncertain efficacy, and may be controversial. May be helpful, not likely to be harmful.

Level IIb: Acceptable, of uncertain efficacy, and may be controversial. Not well established by evidence, can be helpful, and probably not harmful.

Level III: Not acceptable, of uncertain efficacy and may be harmful. Does not appear in guidelines.

Grades Levels of Evidence: Primary (Secondary)

A. Large, randomized trials with clear-cut results (low risk of error)
B. Small, randomized trials with uncertain results (moderate to high risk of error)
C. Nonrandomized, historical and expert opinion; uncontrolled studies, case series

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for "Outpatient Pharmacotherapy of Chronic Obstructive Pulmonary Disease" and "Acute Exacerbation of Chronic Obstructive Pulmonary Disease".

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations.")

Development of the management recommendations relied upon previously published consensus documents and new data from published clinical trials. Consensus articles, meta-analysis, and systematic reviews were included as references for the following topics: smoking cessation, pulmonary rehabilitation, nutritional support, immunizations, and management/prevention of steroid induced osteoporosis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Improved quality of patient care, improved clinical decision-making, and delivery of cost-effective care to veterans with chronic obstructive pulmonary disease(COPD)
- Management of stable COPD aims to avoid or minimize adverse effects of treatment, reduce symptoms, prevent and treat complications, prevent and treat exacerbations, reduce the decline in lung function, improve quality of life, and increase survival.

POTENTIAL HARMS

- Palpitations, tachycardia, chest pain, muscle tremor, dizziness, headache, flushing, difficult urination, or breathing difficulty can occur with oral $beta_2$-

adrenegic agonists. The risk of systemic adverse reactions is increased significantly with oral beta$_2$-agonist agents compared with inhaled agents.
- Ipratropium may cause tachycardia, dry mouth, glaucoma, bladder neck obstruction, or prostatism.
- Theophylline has a narrow therapeutic index with a high risk of dose-related adverse reactions, especially in older patients. Adverse effects of theophylline include insomnia, anxiety, nausea, vomiting, tremor, palpitations, arrhythmias, delirium, and seizures. Older patients have increased susceptibility to chronic theophylline toxicity. Adverse events are greater in patients receiving theophylline in combination with salmeterol
- Drug interactions and other factors altering theophylline metabolism are numerous (Refer to Appendix 4 in the original guideline document).
- Pulmonary status may deteriorate when inhaled steroids are withdrawn from patients who were receiving maintenance therapy with these agents.
- Adverse effects of oral corticosteroids are numerous, including hypertension, hyperglycemia, weight gain, purpura, mental status changes, depression, glaucoma, cataracts, myopathy, and adrenal suppression. Osteoporosis may occur within 6 months.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Regardless of the setting in which patients with chronic obstructive pulmonary disease (COPD) are cared for, the clinician is encouraged to follow these and other COPD guidelines and to use clinical judgment of when to refer to a specialist. This will depend on the skill and experience of managing patients with COPD, and also the resources available to the practitioner.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group. The pharmacologic management of chronic obstructive pulmonary disease. Washington (DC): Veterans Health Administration, Department of Veterans Affairs; 2002 Sep. 31 p. [157 references]

ADAPTATION

Development of the guidelines relied upon the following consensus documents:

- Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. NHLBI/WHO workshop report. www.goldcopd.com
- Bach PB, Brown C, Gelfand SE, American College of Physicians-American Society of Internal Medicine; American College of Chest Physicians. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001; 134:600-20.
- American Thoracic Society Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Resp Crit Care Med 1995; 152:S78-S121.
- British Thoracic Society Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52(suppl 5): Sl-S28.
- Siafakas NM et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD): A consensus statement of the European Respiratory Society (ERS). Eur Respir J 1995; 8:1395-1420.
- Department of Veterans Affairs Clinical Practice Guidelines for the Management of Persons with Chronic Obstructive Pulmonary Disease or Asthma. Publication No. 99-0012.

DATE RELEASED

2002 Sep

GUIDELINE DEVELOPER(S)

Department of Defense - Federal Government Agency [U.S.]
Department of Veterans Affairs - Federal Government Agency [U.S.]
Veterans Health Administration - Federal Government Agency [U.S.]

SOURCE(S) OF FUNDING

United States Government

GUIDELINE COMMITTEE

Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Medical Advisory Panel (MAP) for the Pharmacy Benefits Management Strategic Healthcare Group: C.B. Good, MD, MPH, Chairman, Medical Advisory Panel, Staff Physician, Department of Medicine, VA Pittsburgh Healthcare System, Associate Professor of Medicine, University of Pittsburgh; Thomas Craig, MD, Chief Quality & Performance Officer, Office of Quality & Performance Management, Department of Veterans Affairs, Washington DC; Barry Cusack, MD, Chief, Geriatric Section, VAMC Boise, ID., Associate Professor of Medicine, Division of Gerontology & Geriatric Medicine, School of Medicine, University of Washington; Gregory Dalack, MD, Chief, Psychiatry Service, VA Ann Arbor Healthcare System, Assistant Professor of Psychiatry, University of Michigan; Thomas H. Dickinson, MD, Local Service Line Manager, Ambulatory Care Service Line, VAMC Brockton, MA; LTC John R. Downs, MD, Program Director, Internal Medicine Residency, DoD Pharmacoeconomics Center, Lackland AFB, TX; Michael Ganz, MD, Chief, Nephrology, VAMC Cleveland, Associate Professor in Medicine, Case Western Reserve University; Peter A. Glassman, MBBS, MSc, Staff Internist, Department of Medicine, VA Greater Los Angeles Healthcare System, Assistant Professor of Medicine, University of California, Los Angeles; Matthew Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare Systems; Robert Goodhope, MD, Chief Medical Officer, VA Outpatient Clinic, Tallahassee, FL; Robert J. Hariman, MD, Director, Cardiac Electrophysiology, Hines VA Hospital, Professor of Medicine, Loyola University School of Medicine; William Korchik, MD, Director, Extended Care Center, VAMC Minneapolis, MN., Assistant Professor of Medicine, University of Minnesota; John Pope, MD, Director of Behavioral Health, VA Eastern Kansas Healthcare System, Clinical Assistant Professor, University of Missouri-Kansas City School of Medicine; Alexander Shepherd, MD, Professor of Medicine and Pharmacology, University of Texas Health Science Center, Dept of Pharmacology & Medicine, San Antonio, TX

Pharmacy Benefits Management (PBM) Strategic Healthcare Group (SHG): John E. Ogden, RPh, MS, FASHP, Chief Consultant, PBM SHG, VA Headquarters; Virginia Torrise, PharmD, Deputy Chief Consultant, PBM SHG, VA Headquarters; Michael Valentino, RPh, MHSA, Associate Chief Consultant, PBM SHG; Joseph Canzolino, RPh, Assistant Chief Consultant, PBM SHG; Muriel Burk, PharmD, Outcomes Research Specialist; Fran Cunningham, PharmD, Program Manager for Pharmacoepidemiologic and Outcomes Research; Elaine M. Furmaga, PharmD, Clinical Pharmacy Specialist; Mark C. Geraci, PharmD, BCOP, Clinical Pharmacy Specialist; Francine Goodman, PharmD, BCPS, Clinical Pharmacy Specialist; Cathy Kelley, PharmD, BCPS, Clinical Pharmacy Specialist; Deborah Khachikian, PharmD, Clinical Pharmacy Specialist; Kathryn Tortorice, PharmD, BCPS, Clinical Pharmacy Specialist

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Department of Veterans Affairs Web site.

Print copies: Available from the Department of Veterans Affairs, Veterans Health Administration, Office of Quality and Performance (10Q) 810 Vermont Ave. NW, Washington, DC 20420.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on August 19, 2004. The information was verified by the guideline developer on November 15, 2004.

COPYRIGHT STATEMENT

Date Modified: 2/21/2005